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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/776,669	02/11/2004	Alvin C. Powers	VBLT:033US	3480

32425 7590 06/20/2006

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EXAMINER	
SINGH, ANOOP KUMAR	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/776,669	POWERS ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *April 20, 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on April 20, 2006, has been received and entered. Claims 1, 4, 5, 8, 10, 21, 24, 25 and 29 have been amended.
Claims 1-30 are under consideration in the instant application.

Drawings

The objection to the drawings under 37 CFR 1.83(a) is withdrawn in view of new drawings submitted by Applicant's on April 20, 2006.

Claim Objections

The objection to the claim 29 is withdrawn in view of applicant's amendment to the claim 29.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Applicant's amendment in claims 1, 4, 5, 8, 10, 21, 24 and 25 are found persuasive. Therefore, Claims previously rejected under 35 USC § 112 as being vague and indefinite are withdrawn.

New- Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118(a) states "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application". In the instant case, applicant's amendment of limitation "quality" to "revascularization and the survival" is considered new matter. Applicants do not point to the specification for the specific support of the claimed amendments. Upon further review of the instant specification, examiner could only find support of condition wherein a cell preparation consisting of endothelial and insulin producing cell that is transplanted in the mammal. However, as amended instant claims now reads on *in vitro* and *in vivo* revascularization of endothelial cells. Since specification asserts that endothelial cells from different source will be prepared and recitation of endothelial cell revascularization and survival *in vitro* would be different in scope as compare to original scope intended for preparing cell preparation comprising insulin producing cell and performing steps to increase the quantity and quality of endothelial cell. In absence of any specific definition of quality, it was interpreted as routine culturing of endothelial cells. Furthermore, Examiner could not find a direct or indirect support contemplating that method steps would also involve revascularization of endothelial cells *in vitro* before transplant as recited in claims 1, 4, 5, 21, 24 and 25.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph-written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981) teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time application was filed... If a claim is amended to include subject matter, limitation or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes, "When

an amendment is filed in reply to an objection or rejection based on U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendment made to the disclosure".

To the extent the claimed compositions and or method are not described in the instant disclosure, claims 1-30 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since the applicants disclosure do not teach a composition and/or method that is adequately described in the specification. As described before, the specification does not provide adequate guidance on determining what is included or excluded by the claims as amended and therefore an artisan of skill would require undue experimentation to practice or make and/or use the invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-30 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of transplanting a preparation of autologous pancreatic islet and endothelial cells, the method comprising administering said preparation to a mammal by injecting into hepatic portal vein such that it produces insulin for the treatment of diabetes, however it does not reasonably provide enablement for treating any patient by transplanting any insulin producing cells with any stem or bone marrow or genetically modified endothelial cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claimed invention recite an improved method for transplanting insulin-producing cells for the treatment of diabetes by manipulating the quantity and quality of endothelial cells in the transplanted material. Dependent claims list route of administration and type and source of insulin producing cells. Furthermore, subsequent claims describes endothelial cells are intra-islet endothelial cell, stem or bone marrow derived cells that further limits to genetically modified endothelial cells. It is noted that the intended use of these cells is for the treatment of diabetes by transplantation of these cells in a patient.

The application as filed is not enabling for the invention commensurate with the full scope of the claims because art of gene targeting and cell transplantation in human with stem or bone marrow or genetically modified endothelial cells for the treatment of diabetes was *unpredictable* as has been recognized by the art of skill and therefore require undue experimentation. As will be shown below, the broad aspects as well as limitations were not enabled for the claimed invention commensurate with the full scope of the claims at the time of filling of this application because neither the specification nor the art of record taught sufficient guidance to practice the claimed invention commensurate with the scope of the claim.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ.2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working example are not disclosed in the specification, therefore enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore, skepticism raised in enablement rejections are those raised by the art by artisan of expertise.

The specification as filed provides a general description of endothelial, insulin producing and other cell type and their growth conditions (pp 9-14). Page 9-17 describes genetic engineered endothelial and insulin producing cells. Page 17-25 provides a general description of vectors, tissue specific promoters. Page 26-39 of the specification discloses definition of terms, general description of biological method, method of gene delivery, transfection and a general description of different viral vectors. Rest of the specification teaches a general description of adjunct therapies, in vivo use and devices for delivering the cell based therapies. In summary, the specification does not provide any specific guidance for the claimed invention commensurate with the scope of the claim because the specification as filed does not teach how to many endothelial cells are required, how to differentiate stem cells to endothelial stem cells or endothelial cells. Furthermore, It is noted that the specification does not provide any guidance as to how endothelial cells particularly stem or bone marrow derived cells would be genetically modified for the use in the host as cell therapy. The method of transplanting endothelial cell derived from stem or bone marrow in human was not routine, rather was unpredictable at the time of filing of this application as neither art of record nor the specification teaches how to practice the claimed inventions.

Specification's examples 1-2 on pages 48-56 disclose the expression of endothelial cell marker in isolated islet. This observation is followed by an experiment wherein inventor utilizes a model in which endothelial cells are tagged with Lac Z to show that lac Z expression recapitulate expression of Flk-1. Furthermore, inventor discloses in three different types of transplants that the islets are vasuclarized within the surrounding of islet graft. It also discloses that both donor and recipient endothelial cells are found within the islet graft area positive for insulin. These studies show that intra islet endothelial cells survive and contribute to revascularization process. Using the islet

graft sections, it is further shown that the capillaries formed are either donor or recipient endothelial cells and chimeric blood vessels are formed from the mixture of donor and recipient endothelial cells. It also suggest revascularization of graft involves approximately 40% of the endothelial cells from the donor islet.

Although the specification show the role and importance of endothelial cells during successful islet transplantation, however these disclosures do not demonstrate the information required by the Artisan to reasonably predict the optimal number endothelial cells and insulin producing cells required for successful transplantation in the host mammal. The specification does not provide any specific guidance of any correlation between the number of insulin producing cells and endothelial cell that is required for the successful transplant. In other words, the art did not teach and was unpredictable at the time of invention, as to how many endothelial and insulin producing cells would be sufficient to produce insulin.

Specification does not provide disclosure on number of endothelial cell that are transplanted to elicit specific response. In absence of such guidance, an artisan of the skill of the art would have to do undue experiment to determine the precise amount of therapeutic composition needed to a patient. Although much will be dependent upon the specific requirement of the patient, however, without any specific guidance on how much insulin could be produced after transplanting preparations of islet and endothelial cell will not be enabling for the use in humans.

Next, claimed invention encompasses hepatocytes, neurons, myocytes or genetically modified cells as insulin producing cells. Transplantation of these cells in any patient and use of genetically modified non endocrine cells that could produce insulin was not routine at the time of filing of this application.

The state of the prior art effectively summarized by the reference of Giannoukakis et al., (2002: BioDrugs 16(3) 149-173) state that more work is required to make hepatocytes or other non endocrine cells into fully surrogate β cells (pp163, col.1, paragraph 2). Giannoukakis et al states that gene and cell therapy strategies have been shown to be effective in preventing and treating type I diabetes in rodents and prolonging allograft survival in rodents and non human primate" (pp 167, paragraph 3).

In summary at the time of invention, the art of hepatocytes, neuron, myocytes or genetically engineered cells as insulin producing cell was unpredictable and the specification does not provide any specific guidance as to how these modified cells would have been transplanted in humans. In addition, prior art at the time of filing of this application as described before did not provide any convincing guidance in this regard either.

Rafii et al., reviewed one year after filing of this application the state of the art of therapeutic stem cells and progenitor cell transplantation for organ vascularization and observed, "Despite the contribution of bone marrow cells in tissue revascularization in animal models, the significance of these cells in restoring organ vascularization remains unknown (pp 703, 1st paragraph). Several recent studies have challenged the potential of bone marrow-derived cells in restoring vasuclarization.... "The success of these strategies depends on defining the mechanisms by which stem and progenitor cells undergo appropriate molecular induction to direct their proliferation, mobilization and differentiation, thereby permitting their functional incorporation into adult tissue." It is noted that contamination in preparations, factors that promote differentiation, route of delivery of stem cells may play a critical role in the outcome of tissue vascularization (pp 709, entire page).

It is noted, the specification is not enabling for practicing the claimed method of using any stem or bone marrow cells. The specification, does not disclose therapy guidance as to how would the method of ex vivo cell therapy would be carried out. For example, the specification does not provide any example or evidence as an artisan of skill would have been able to use stem or bone marrow cells for transplantation in human or number of cells that would be used for the therapy.

As shown above, the broad aspects as well as limitations were not enabled for the claimed invention at the time of filling of this application because neither the specification nor the art of record taught sufficient guidance to practice the claimed invention. The application fails to provide enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to (i) how an artisan of skill would have practiced the claimed method, (ii) the claimed method would have

resulted in providing the increase number of endothelial cell in appropriate amount during the transplantation of insulin producing cell for the treatment of diabetes. An artisan would have required to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because art of stem cell, gene therapy and cell transplantation *in vivo* was unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced.

In conclusion, in view of breadth of the claims and absence of a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for the claimed inventions commensurate with the full scope of the claims. The specification and prior art do not teach a method of transplanting insulin-producing hepatocytes, neuron, myocytes or genetically engineered cell in humans. Furthermore, specification also fails to provide any guidance on *transplanting* endothelial cells, which are immortalized or derived from stem or bone marrow in humans. An artisan of skill would have required undue experimentation to develop/design a suitable vector and practice the method as claimed because the art of gene therapy, vector design and *in vivo/ex vivo* delivery and treatment of diabetes condition in general by cell therapy *in vivo* was unpredictable at the time of filling of this application as supported by the observations in the art record.

Response to Arguments

Applicant arguments filed on 3/20/2006 have been fully considered but they are not persuasive. Applicant in their argument on page 6 and 7, state that examiner acknowledges that there was showing of islet cell survival leading to insulin production and vascularization involving endothelial cells. The applicants further argue that this a prima facie evidence of enablement and examiners only rebuttal is that optimal insulin producing cell is not provided. The applicant's also assert that objective evidence that breadth of insulin producing cells are missing from the record.

In response, it is emphasized that amended claims of instant invention encompasses hepatocytes, neurons, myocytes or genetically modified cells as insulin producing cells. Transplantation of these cells in any patient and use of genetically modified non endocrine cells that could produce insulin was not routine at the time of filing of this application as stated in previous office action dated 10/20/2005 on page 8, para 2 and 4. The specification provides a description that is not sufficient to provide enabling support because the claimed therapy method cannot be actually reduced to practice commensurate with full scope of the claim until the skilled artisan is provided by sufficient guidance.

The cited reference of Giannoukakis et al (Biodrugs, 2002, 149-173, especially pp 163, col. 1, para 2) clearly describes several limitation and problem in using variety of cells that are engineered to produce insulin for possible alternatives to islet transplant and concludes that "despite the promising approaches more work is needed to make heaptocytes or other non endocrine cells into fully surrogate β cells (supra). Giannoukakis et al describe that the response to glucose in not as rapid as that found in β cells, Secondly, the non β cells glucose sensitive promoters have elements that respond to hormonal and metabolic signals which can impede or abrogate the desired objective of tight glucose regulation. Thirdly, Giannoukakis describes that the problem with existing promoters is that requires GK-dependent phosphorylation of glucose, an activity that is insulin dependent. It is emphasized that Giannoukakis concludes that combination of different glucose responsive hepatic gene may be needed to create an optimal synthetic promoter to drive hepatic insulin expression (pp 163, para 2). Thus, it was apparent from the cited reference that a number of issues remained unanswered in using genetically modified insulin producing cells for transplants. The specification does not provide any example or describes critical elements in sufficient details that would have been required in order to use genetically modified non-β cells for the transplant. An artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because of the art of genetically modified non β cells to produce insulin for pancreatic transplant was not

routine rather it was unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced using any genetically modified insulin producing cells as recited in claims.

In addition, cited reference of Rafii et al., reviewed the art recognized limitation of therapeutic stem cells and progenitor cell transplantation for organ vascularization one year after filing of instant application as stated in previous office action dated 10/24/2003, page 10, para 1. Rafii describes contamination in preparations of stem cells, factors that promote differentiation, route of delivery of stem cells as few critical factors that would play a role in the successful outcome of tissue vascularization (pp 709, entire page). Rafii et al state that most studies have characterized endothelial progenitor cells by their capacity to take up Ac-LDL, express PECAM (CD31) or bind lectins, phenotypic features that are also shared by monocytic cells. In addition, cultured EPCs and CEPs do not readily differentiate into adherent endothelial monolayers, but require 10–20 days with appropriate stimuli to mature into plastic-adherent endothelium. The mechanisms for differentiation of EPCs and CEPs into functional mature vessels *in vivo* are complex and are mediated through interaction with as-yet-unrecognized, tissue-specific growth factors, proteases and matrix proteins. Rafii et al also describe that exposure to organ-specific angiogenic and matrix factors may be necessary to program EPCs and CEPs to home and incorporate into a particular tissue. Lastly, Rafii emphasizes that route of delivery of stem cells may have a critical role in the success of tissue vascularization. The specification does not provide adequate guidance how stem or other progenitor cells will be characterized or how it would be differentiated to a specific cell linage. In addition, specification also fails to provide any specifics in terms of culture condition and route of administration of stem or bone marrow cells that are contemplated for enhancing vascularization.

In absence of any such explicit teaching, a skilled artisan would have to determine the various specifics and would have to perform undue experimentation to obtain stem or bone marrow cells from same or different donor, characterize and use them for transplant. The cited art teaches several problems associated with characterization, contamination, differentiation, homing and route of delivery of

stem/bone marrow cells in enhancing vascularization. These would have required undue experimentation because neither the specification nor the art of record provided any specific guidance in this regard.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4, 7-8, 10-12, 21-24, 26 remain rejected under 35 U.S.C. 102(e) as being anticipated by Revazova and Sebastian (US Patent Publication US2003/0113302A1 publication date 6/19/2003, filing date 8/30/2002).

Revazova et al teaches a method of transplanting tissue into a recipient to increase vascularization of the tissue by administering the endothelial cell and the tissue to the transplanted site (pp4; claim 1). The inventors also disclose that the tissue transplant is a pancreatic islet cells that is transplanted for the treatment of diabetes (pp 3; paragraph 30 and 31). Furthermore, the inventors also teaches combining tissue transplant with recipient endothelial cell either before or during transplantation and the transplantation method involves tissue contact with endothelial cell prior to transplant (pp 3; paragraph 33, 38 and 39). It is noted that optimization of endothelial cell quantity and quality, while propagating the cell culture is inherent in the teaching of Revaova et al. They also disclose use of immunosuppressive agents, growth factors and other substances with endothelial cells and/or transplant (pp4; paragraph 41). The invention also reads on to a method of treating humans with diabetes by transplanting autologus or allogenic islet and recipient endothelial cell (pp2 paragraph 22). In addition, the inventor demonstrates the effectiveness of transplantation of islet cells and endothelial

cells. The data in rodent model suggest that only the recipient endothelial cell could stimulate vessel formation in tissue transplant, whereas non-recipient endothelial cell had no effect on vascularization (example, paragraph 42-48).

Therefore, the claimed invention is anticipated by Revazova and Sebastian.

Response to Arguments

Applicant's arguments filed April 20, 2006 have been fully considered but they are not persuasive. Applicants argue that the title of cited publication (US Patent application no 2003/0113302A1) is use of recipient endothelial cells for enhanced vascularization of tissues, which constitutes a teaching away from the present invention that relies on donor endothelial cells.

In response to applicant's argument it is emphasized that that the features upon which applicant relies (i.e., donor endothelial cells) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Furthermore, contrary to the applicants argument, cited reference teaches role of using recipient endothelial cell as well as donor cells (non-recipient endothelial) in vascularization (example, paragraph 42-48, supra). In addition, rejected claims 1-4, 7-8, 10-12, 21-24, 26 recite a method for transplanting insulin producing cells comprising (1) providing a cell preparation comprising insulin producing cell (ii) performing one or more steps that increases quantity and/or revascularization and the survival of endothelial cells and (iii) transplanting cells of said preparation into a host mammal. The cited reference ('302) teaches all the three steps by transplanting a cell comprising the insulin producing cells and endothelial cells. Applicants also argue about inherency in handling of endothelial cells and further states that no support is provided for a teaching of culturing to improve survival or quality of the endothelial cells is provided

In response, it is noted that cited publication teaches use of growth factor with endothelial cells and/or transplant (supra). Thus, any beneficial effects of growth factor

on endothelial cells are inherent in the teaching of cited publication. Furthermore, contrary to applicants argument, example (paragraph 42-48, supra) of cited publication teaches culturing of microvascular endothelial cells in presence of EGM medium supplemented with bovine brain extract-BBE. Once again, art recognized beneficial effects of BBE or even culture medium are inherent in the growth and survival of endothelial cells.

Withdrawn- Claim Rejections - 35 USC § 103

Applicant's arguments see pages 9-10, filed April 20, 2006, with respect to claims 1-4, 6-18, 21-24, 26 –30 have been fully considered and are persuasive due to lack of motivation to combine references. The rejection of claims 1-4, 6-18, 21-24, 26 –30 has been withdrawn.

Conclusion

No Claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:
Osborne and Nagarajan (US Patent 6537806, dated 3/25/2003 filing date 11/4/1998); Kalka et al (Proc Natl Acad Sci U S A. 2000; 97(7): 3422-3427) and Ryan et al., (Diabetes 2002, 51(7): 2148-2157).

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272- 0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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